DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 177

[Docket No. 93F–0319]

Indirect Food Additives: Polymers

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of hydrogenated butadiene/acrylonitrile copolymers, intended for contact with food in repeated use applications. This action is in response to a petition filed by Zeon Chemicals, Inc.

DATES: This rule is effective [*insert date of publication in the* **Federal Register**]. Submit written objections and requests for a hearing by [*insert date 30 days after date of publication in the* **Federal Register**]. The Director of the Office of the Federal Register approves the incorporations by reference in accordance with 5 U.S.C. 552(a) and 1 CFR 51 of certain publications in § 177.2600(c)(4)(i) (21 CFR 177.2600(c)(4)(i)), as of [*insert date of publication in the* **Federal Register**].

ADDRESSES: Submit written objections to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Andrew J. Zajac, Center for Food Safety and Applied Nutrition (HFS–215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3095.

SUPPLEMENTARY INFORMATION:

I. Background

In a notice published in the **Federal Register** of October 4, 1993 (58 FR 51632), FDA announced that a food additive petition (FAP 3B4377) had been filed by Zeon Chemicals, Inc., Three Continental Towers, suite 1012, 1701 Golf Rd., Rolling Meadows, IL 60008 (now 4111 Bells Lane, Louisville, KY 40211). The petition proposed to amend the food additive regulations to provide for the safe use of acrylonitrile-butadiene copolymer, hydrogenated, intended for contact with food in repeated use applications. (The additive is currently listed in the regulation under the nomenclature hydrogenated butadiene/acrylonitrile copolymers, and this nomenclature will be retained.)

In FDA's evaluation of the safety of this food additive, the agency reviewed the safety of the additive itself and the chemical impurities that may be present in the additive resulting from its manufacturing process. Although the additive itself has not been shown to cause cancer, it has been found to contain residual amounts of acrylonitrile and butadiene as impurities resulting from its manufacture. These chemicals have been shown to cause cancer in test animals. Residual amounts of impurities are commonly found as constituents of chemical products, including food additives.

II. Determination of Safety

Under the general safety standard of section 409(c)(3)(A) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348(c)(3)(A)), a food additive cannot be approved for a particular use unless a fair evaluation of the data available to FDA establishes that the additive is safe for that use. FDA's food additive regulations (21 CFR 170.3(i)) define safe as ''a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.''

The food additives anticancer, or Delaney, clause of the act (21 U.S.C. 348(c)(3)(A)) provides that no food additive shall be deemed safe if it is found to induce cancer when ingested by man or animal. Importantly, however, the Delaney clause applies to the additive itself and not to

impurities in the additive. That is, where an additive itself has not been shown to cause cancer, but contains a carcinogenic impurity, the additive is properly evaluated under the general safety standard using risk assessment procedures to determine whether there is a reasonable certainty that no harm will result from the intended use of the additive. (Scott *v.* FDA, 728 F.2d 322 (6th Cir. 1984.))

In evaluating the safety of a food additive, FDA customarily reviews the available data on each relevant chemical impurity to determine whether the chemical induces tumors in animals or humans. If FDA concludes that the chemical impurity causes cancer in animals or humans, the agency calculates the unit cancer risk for the chemical and the upper bound limit of lifetime human cancer risk from the chemical's presence in the additive (Ref. 1).

In some instances, the available data and information may not allow the agency to determine whether a particular chemical impurity is a carcinogen. However, the available data may suggest, but not establish definitively, that the impurity poses a human cancer risk. In such circumstances, the agency may perform a risk assessment based upon the assumption that the impurity is carcinogenic. This approach permits the agency to determine whether there is a reasonable certainty that no harm will result from the petitioned use of the additive, even though the carcinogenic status of the impurity is not clearly established.

FDA followed this approach to determine whether there is a reasonable certainty that no harm will result from the use of hydrogenated butadiene/acrylonitrile copolymers; in so doing, FDA assumed that butadiene, an impurity in the additive, is a human carcinogen. In inhalation studies, butadiene has been reported to induce, in mice and rats, tumors at the site of exposure (lungs) as well as a variety of tumors at numerous other sites (Refs. 2 to 4). However, FDA does not believe that these inhalation studies are necessarily determinative of the carcinogenic potential of butadiene when administered orally, the most likely route of human exposure to food additives. Because no long-term studies are available in which butadiene was administered orally, the agency performed a risk assessment for butadiene based on a twofold assumption: That butadiene would

induce tumors in animals and humans if administered orally and that its potency by the oral route of exposure would be no greater than its potency by the inhalation route of exposure. In FDA's view, this is a conservative assumption (Ref. 5). Using this procedure, FDA estimated the upper bound limit of lifetime human cancer risk from butadiene under the proposed conditions of use of hydrogenated butadiene/acrylonitrile copolymers.

III. Safety of the Petitioned Use of the Additive

FDA estimates that the petitioned use of the additive, hydrogenated butadiene/acrylonitrile copolymers, will result in exposure to no greater than 5 parts per trillion of the additive in the daily diet (3 kilograms (kg)) or an estimated daily intake of 15 nanograms per person per day (ng/p/d) (Ref. 6).

FDA does not ordinarily consider chronic toxicological studies to be necessary to determine the safety of an additive whose use will result in such low exposure levels (Ref. 7), and the agency has not required such testing here. However, the agency has reviewed the available toxicological data on the additive and concludes that the estimated small dietary exposure resulting from the petitioned use of this additive is safe.

FDA has evaluated the safety of this additive under the general safety standard, considering all available data and, as noted above, using risk assessment procedures to estimate the upper-bound limit of lifetime human risk presented by acrylonitrile and butadiene, the carcinogenic chemicals that may be present as impurities in the additive. The risk evaluation of acrylonitrile and butadiene has two aspects: (1) Assessment of exposure to the impurities from the petitioned use of the additive, and (2) extrapolation of the risk observed in animal bioassays to the conditions of exposure to humans.

A. Acrylonitrile

FDA has estimated the exposure to acrylonitrile from the petitioned use of the additive as a component of repeated use food-contact articles to be no more than 0.095 parts per trillion in

the daily diet (3 kg), or 0.29 ng/p/d (Ref. 6). The agency used data from a long-term rodent bioassay on acrylonitrile conducted by Quast et al. (Ref. 8) to estimate the upper-bound limit of lifetime human risk from exposure to this chemical resulting from the petitioned use of the additive. The authors reported that the test material caused astrocytomas of the nervous system, papillomas and carcinomas of the tongue, papillomas and carcinomas of the stomach, and Zymbal's gland carcinomas in male and female rats. The authors also reported carcinomas of the small intestine and the mammary gland in female rats.

Based on the agency's estimate that exposure to acrylonitrile will not exceed 0.29 ng/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the petitioned use of the subject additive is 5.45×10^{-10}, or 0.5 in a billion (Ref. 9). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to acrylonitrile is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to acrylonitrile would result from the petitioned use of the additive.

B. Butadiene

The scientific literature contains a variety of information regarding the carcinogenic potential of butadiene. As noted, in a long-term inhalation study butadiene has been reported to induce a variety of tumors including in the hematopoietic system, heart, lung, forestomach, liver, Harderian gland, brain, and kidney in male and female mice and tumors of the ovaries and mammary gland in female mice (Ref. 2). Butadiene also has been reported to induce tumors of the pancreas and testis in male rats and tumors of the uterus, mammary gland, and thyroid in female rats in a long-term inhalation study (Refs. 3 and 4).

No long-term studies are available in which butadiene was administered to test animals orally. Generally, FDA does not rely on inhalation studies to assess the potential carcinogenicity and cancer potency of substances in food, for which the most likely route of human exposure is oral.

However, in order to determine whether there is a reasonable certainty that no harm would result from the presence of butadiene as an impurity in the subject additive, the agency has assumed that butadiene is an oral carcinogen and has performed a worst-case risk assessment of the carcinogenic potential of butadiene using data from the inhalation study on female mice. FDA has relied on this study because it is the sex, species, and study that demonstrated the highest unit cancer risk for butadiene.

FDA has estimated the exposure to butadiene from the petitioned use of the subject additive would not exceed 0.0016 part per trillion in the daily diet (3 kg), or 4.8 picogram per person per day (pg/p/d) (Ref. 6). Based on this estimate and the assumption that butadiene would induce tumors with the same potency in an oral study as it did in the mice inhalation study, FDA estimates that the upper-bound limit of lifetime human risk from butadiene exposure as a result of the petitioned use of the subject additive would be 1.12×10^{-10}, or 0.1 in a billion (Refs. 5 and 10). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to butadiene is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to butadiene would result from the petitioned use of the additive.

C. Need for Specifications

The agency also has considered whether specifications are necessary to control the amount of acrylonitrile and butadiene as impurities in the food additive. The agency finds that specifications are not necessary for the following reasons: (1) Because of the low levels at which acrylonitrile and butadiene may be expected to remain as impurities following production of the additive, the agency would not expect these impurities to become components of food at other than extremely low levels; and (2) the upper-bound limits of lifetime human risk from exposure to acrylonitrile and butadiene are very low, 0.5 in a billion and 0.1 in a billion, respectively.

IV. Conclusion

FDA has evaluated data in the petition and other relevant material. Based on this information, the agency concludes that: (1) The proposed use of the additive in repeated use food-contact articles is safe, (2) the additive will achieve its intended technical effect, and therefore, (3) the regulations in § 177.2600 should be amended as set forth below.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person listed above. As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

V. Environmental Impact

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

VI. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Objections

Any person who will be adversely affected by this regulation may at any time file with the Dockets Management Branch (address above) written objections by [*insert date 30 days after date of publication in the* **Federal Register**]. Each objection shall be separately numbered, and each

numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Lorentzen, R., ''FDA Procedures for Carcinogenic Risk Assessment,'' *Food Technology*, vol. 38, pp. 108–111, 1984.

2. ''Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106–99–0) in B6C3F1 Mice (Inhalation Studies),'' National Toxicology Program, Technical Report Series, No. 434.

3. Owen, P. E. et al., ''Inhalation Toxicity Studies with 1,3-Butadiene. Two Year Toxicity/ Carcinogenicity Study in Rats,'' *American Industrial Hygiene Association Journal*, 48:407–413, 1987.

4. Owen, P. E. et al., ''Inhalation Toxicity and Carcinogenicity Study of 1,3-Butadiene in Sprague-Dawley Rats,'' *Environmental Health Perspectives*, 86:19–25, 1990.

5. Memorandum dated March 3, 2000, from the Division of Health Effects Evaluation to the Chairman of the CFSAN Cancer Assessment Committee and Quantitative Risk Assessment Committee, ''A worst-case estimate of human cancer risk from exposure to 1,3-butadiene as an impurity in all approved and

petitioned uses of 1,3-butadiene-based polymers in food-contact applications, and in several petitioned food additives and pre-market notifications.''

6. Memorandum dated March 25, 1994, from Chemistry Review Branch to Indirect Additives Branch, ''FAP 3B4377 (MATS# 711, M2.1)—Zeon Chemicals, Inc. Submission dated 4–21–93. Hydrogenated acrylonitrile butadiene elastomers (HNBR) as components of repeat-use articles.''

7. Kokoski, C. J., ''Regulatory Food Additive Toxicology,'' in *Chemical Safety Regulation and Compliance*, edited by F. Homburger, and J. K. Marquis, New York, NY, pp. 24–33, 1985.

8. Quast, J. F., C. E. Wade, C. G. Humiston, R. M. Carreon, E. A. Hermann, C. N. Park, and B. A. Schwetz, ''A Two Year Toxicity and Oncogenicity Study With Acrylonitrile Incorporated in the Drinking Water of Rats,'' Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical USA, Midland, MI 48640, final report dated January 22, 1980, corrections dated November 17, 1980.

9. Memorandum dated July 10, 2000, from the Division of Health Effects Evaluation to the Division of Petition Control, ''FAP 3B4377: Worst-Case Cancer Risk Assessment for Acrylonitrile.''

10. Memorandum dated April 3, 2000, from the Division of Petition Control to the Quantitative Risk Assessment Committee, ''Estimation of the Upper-Bound Lifetime Risk for Butadiene—FAP 3B4377.''

List of Subjects in 21 CFR Part 177

Food additives, Food packaging, Incorporation by reference.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 177 is amended as follows:

PART 177—INDIRECT FOOD ADDITIVES: POLYMERS

1. The authority citation for 21 CFR part 177 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 348, 379e.

2. Section 177.2600 is amended in paragraph (c)(4)(i) by revising the entry for ''Hydrogenated butadiene/acrylonitrile copolymers'' to read as follows:

§ 177.2600 Rubber articles intended for repeated use.

* * * * *

(c) * * *

(4) * * *

(i) * * *

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Hydrogenated butadiene/acrylonitrile copolymers (CAS Reg. No. 88254–10–8) produced when acrylonitrile/butadiene copolymers are modified by hydrogenation of the olefinic unsaturation to leave either: (1) Not more than 10 percent *trans* olefinic unsaturation and no α, β-olefinic unsaturation as determined by a method entitled "Determination of Residual α, β-Olefinic and Trans Olefinic Unsaturation Levels in HNBR," developed October 1, 1991, by Polysar Rubber Corp., 1256 South Vidal St., Sarnia, Ontario, Canada N7T 7MI; or (2) 0.4 percent to 20 percent olefinic unsaturation and Mooney viscosities greater than 45 (ML 1 + 4 @ 100 °C), as determined by ASTM Standard Method D1646–92, "Standard Test Method for Rubber—Viscosity and Vulcanization Characteristics (Mooney Viscometer)," which are both incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies of these methods may be obtained from the Division of Petition Control (HFS–215), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington,

DC, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC. A copy of ASTM Standard Method D1646–92 may also be obtained from the American Society for Testing and Materials, 100 Barr Harbor Dr., West Conshohocken, PA 19428–2559.

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Dated: 11/6/00
November 6, 2000

Margaret M. Dotzel
Associate Commissioner for Policy

[FR Doc. 00–???? Filed ??–??–00; 8:45 am]

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